Desmosome

# Desmoplakin Is Essential for Epidermal Sheet Formation

Gemma Hopkins[1], Tomomi E. Kimura[1] and David R. Garrod[1]

[1]*Faculty of Life Sciences, University of Manchester, Manchester, UK.*

*Correspondence: D. David R. Garrod, david.garrod@manchester.ac.uk*

*Published online 30 January 2007. doi:10.1038/sj.skinbio.6250005*

Vasioukhin *et al*. (2001) provided a dramatic demonstration that the desmosomal cytolinker protein desmoplakin (Dp) is essential for maintaining the integrity of epithelial cell sheets. Furthermore, they show a requirement for desmosomes in efficient maturation of adherens junctions (AJs).

Dp belongs to the plakin family and contains a carboxy-terminal tail incorporating the intermediate filament (IF) binding site and a desmosome association site in the amino-terminal domain. Early embryonic lethality at E6.5 had previously demonstrated the crucial importance of Dp (Gallicano *et al*., 1998). Lethality was due to the breakdown in IF association with desmosomes and the failure of desmosomes to assemble and stabilize. Rescue of this lethal phenotype was achieved by fusion of knockout (KO) and wild-type embryos. This restored $Dp^{+/+}$ extraembryonic tissue postponing lethality to E10 with defects in the heart, neuroepithelium and skin. The microvasculature does not contain desmosomes but was also affected because of disruptions to endothelial junctions comprising Dp, plakoglobin and VE-cadherin (Gallicano *et al*., 2001).

The breakthrough with Dp came from the generation of mice with conditional KO of Dp in the epidermis by Vasioukhin and co-workers. The skin of newborns was very fragile and peeled off with mild mechanical stress, leading to death within a few hours. The number and size of desmosomes corresponded to wild type, but they differed ultrastructurally, lacking an inner dense plaque and attachment to the keratin cytoskeleton, which thus became detached from the cell periphery. This led to disruptions of the epidermis through loss of cell–cell adhesion.

Studies on cultured KO keratinocytes unveiled additional differences, as these were incapable of sheet formation owing to inefficient clustering of desmosomal and AJ components at cell–cell borders. Rescuing with full-length Dp restored desmosome–IF connections, but expression of only the head domain did not, supporting the need for the IF-binding site and desmosome–IF connections in epidermal sheet formation.

The discovery of a patient who was compound heterozygous for Dp mutations causing severe skin fragility reinforces this Dp function (Jonkman *et al*., 2005). The mutations led to a truncation of Dp at the carboxyl terminus rather than complete absence of Dp. This gave rise to a loss of desmosome–IF connections and consequent severe fragility of the skin and mucous membranes, with a substantial loss in body fluids. Early postnatal death ensued.

Vasioukhin *et al*. (2001) also revealed the interdependence of adherens junctions (AJs) and desmosomes. AJs precede and are required for desmosome formation but the ablation of Dp caused a reduction in the number of AJs. This has led to a hypothesis that desmosomes act as molecular clamps holding immature AJs in place for a second phase of maturation during epithelial sheet formation. The integrity of the epidermis is essential for survival, and Dp plays a key role in this vital function.

## TO CITE THIS ARTICLE

Hopkins G *et al*. (2007) Desmoplakin is essential for epidermal sheet formation. *J Invest Dermatol* 127:E12

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